FA family newsletter

A Semi-Annual Newsletter On Fanconi Anemia For Affected Families, Caring Physicians & Research Scientists.

NEWSLETTER #13 **JANUARY, 1993**

Scientific Workshop Explores Progress

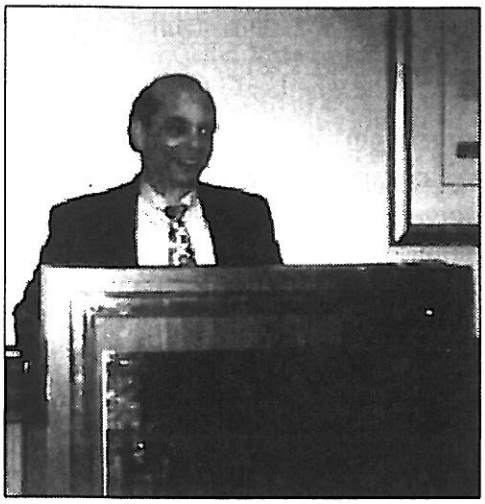
Our fourth annual scientific conference met in Bethesda, Maryland November 23-24, 1992. The Fanconi Anemia Research Fund co-sponsored this workshop with the National Heart, Lung and Blood Institute of the influential National Institutes of Health (NIH).

This conference - the largest medical and scientific meeting on FA ever held — brought 100 participants, including twenty from outside the United States. Researchers or clinicians from Canada, the United Kingdom, France, Italy, Brazil, The Netherlands and Germany attended.

Twenty-three scientific presentations in five major sessions covered topics ranging from basic molecular science to progress in developing future therapies. The insert Report: Workshop on Molecular, Cellular, and Clinical Aspects of Fanconi Anemia summarizes this meeting.

We attended all presentations and an evening "poster session" where 28 new scientific reports on FA were displayed. Here are some impressions:

- The world of FA research is rapidly expanding. As we fervently hoped, scientific attention to this disorder is increasing, especially since Dr. Buchwald's discovery of an FA gene last year. We believe other FA genes will be discovered in the near future.



Alan Levine, Ph.D., Chief of Blood Diseases, NIH, addresses Scientific Conference.

- The co-sponsorship of NIH brings new visibility to FA science.
- Gene therapy for FA is no longer a science fiction dream. Dr. Nienhuis and his NIH colleagues are presently exploring FA as a candidate disease for gene transfer therapy.

Continued on Page 8 (See Workshop)

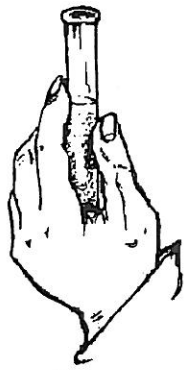
Third Family Meeting Planned

The Third FA Family Symposium will be held in Bloomington, Minnesota on July 16, 17 and 18. We hope you can come!

Whether you have been dealing with this illness for many years or just a few days, we welcome and encourage your attendance. We planned our agenda with you in mind. Recommendations from the past two family symposia have been incorporated into this program. Experts will speak about a broad spectrum of medical issues. Equally important, we have doubled your opportunity to attend small discussion groups. You can share ideas and help deal with some of the

Continued on Page 3 (See Meeting).

Highlights



MEDICAL NEWS

NIH Gene Therapy Advances

We include, with enormous excitement, the report from physicians at NIH which describes advances in gene therapy research for Fanconi anemia. This report underscores the vital importance of testing blood or skin samples of each FA patient to see if the patient belongs to the one "complementation group" for which a gene has been identified. (See offer of Dr. Markus Grompe, Newsletter #11, p. 2). This test potentially may help the patient to be considered for an early gene therapy trial.

Novel Approaches to the Treatment of Fanconi Anemia

Johnson M. Liu, M.D. and Neal S. Young, M.D.

I thank the Fanconi Anemia Research Fund for the opportunity to describe our research at the National Heart, Lung, and Blood Institute, Intramural Division. As you know, we have investigated bone marrow failure disorders, including Fanconi anemia (FA), for many years. Dr. Manuel Buchwald's recent cloning of the Fanconi anemia complementation group C (FACC) gene is a major achievement which suggests new approaches to the treatment of FA.

Current FA treatment approaches are limited. Pancytopenia of FA can be cured by bone marrow transplantation from an HLA-matched sibling. Unfortunately, many patients do not have an appropriate marrow donor. For these reasons, we are interested in developing clinical protocols which do not involve marrow transplantation from another person.

Our work will focus on correction of the FA defect by gene therapy, i.e., by introducing the normal FACC gene into cells from patients who have defective FACC genes of their own. We will attempt correction by using viruses to carry the normal gene into the nucleus of the defective cell. Our goal is to reintroduce these genetically corrected bone marrow cells into the patient's marrow. If successful, this should improve the function of that patient's bone marrow.

Although we are in the early stages of this work, we are currently seeking FA patients regardless of complementation group to participate in a new clinical protocol. In our study, we will be treating patients with a blood-stimulating growth factor known as G-CSF. Our purpose is to determine whether G-CSF can increase the number of very primitive bone marrow cells in the blood of an FA patient. We would then test whether our viral vectors are capable of infecting these primitive bone marrow cells. I emphasize that this first protocol is not designed to cure the patient. We are seeking participants for research which might lead to effective gene therapy protocols in the future.

If you wish to be part of our study, please contact one of us at the following address:

Clinical Hematology Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
Building 10, Room 7C103
Bethesda, MD 20892
(301) 496-5093

Marrow Transplant Registry Planned

Dr. Richard Harris of the Bone Marrow Transplant Unit at the Children's Hospital Medical Center in Cincinnati is initiating a registry of all FA patients in the USA and Canada who have received a bone marrow transplant.

The goal of the registry is to provide information which will help define the best approach for BMT in patients with FA. Dr. Harris is trying to put into the registry every single patient in North America who has undergone BMT, whether the patient survived or not. He has obtained data from his own cent[illegible] and from the Fred Hutchinson Can[illegible] Research Center in Seattle, the International Bone Marrow Transplant Registry and the National Marrow Donor Program. He believes there are several patients who have been transplanted who are not included in any of these registries.

Patients need not be identified by name. But Dr. Harris wants to insure that every patient is in the registry and that no patient is registered in duplicate. Each patient will be uniquely identified by his or her date of birth, date of marrow transplant, and the transplant center.

The database will help define the best preparative therapy for the transplant, the best graft vs host disease prophylaxis, the ideal timing for the transplant when a matched sibling donor is available, or when only a partially matched relative or an unrelated donor is available. The registry will determine the outcomes based on the source of the donor marrow, the degree of match with the recipient, th[illegible] preparative therapy, and the GVHD pr[illegible] phylaxis. Many other crucial factors will be looked at as well.

The information will be presented in this newsletter in addition to being presented at medical meetings.

Please fill out the enclosed questionnaire entitled "Fanconi Anemia Transplant Registry" and return to: Dr. Richard E. Harris, Bone Marrow Transplant Program, Hematology/Oncology Division, Children's Hospital Research Foundation, CHRF 2385, Elland and Bethesda Avenues, Cincinnati, OH 45229-2899. This will help identify every patient in North America who has undergone BMT for FA.

Please remember that presentations and articles will not identify any patient by name or other identifiers. Data will be presented in aggregate only. Each patient will be identified by a unique patient number based on his or her date of birth, date of transplant, and center where the transplant was performed.

Meeting *(Continued from page 1)*
emotional and social issues surrounding this illness.

See enclosed "Fanconi Anemia Family Symposium" for details.

This is the last year the Family Meeting will be supported by the Meyer Memorial Grant. We will try to secure funding for future meetings, but there is no guarantee. We hope you will make a special effort to attend this informational symposium.

Editors' Note and Disclaimer
Statements and opinions expressed in this Newsletter are those of the authors and not necessarily views of the editors or sponsoring Fund. Information provided in this Newsletter about medications, treatments or products should not be construed as medical instruction or scientific endorsement. Always consult your physician before taking any action based on this information.

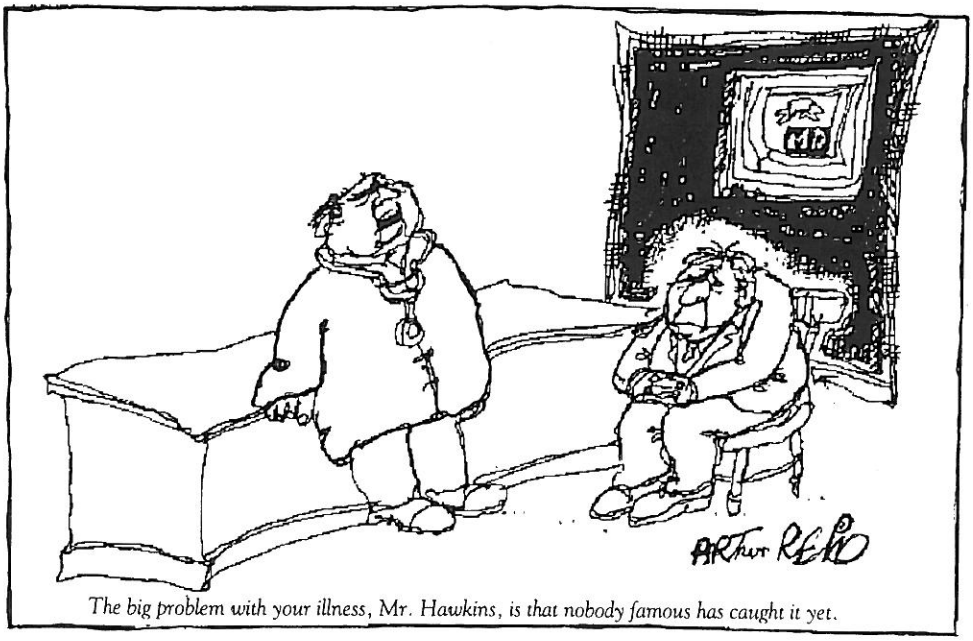
Dr. Nasrollah Shahidi has generously offered to be the Medical Advisor to the FA Family Newsletter. We welcome his contribution to this effort.

Fanconi Anemia After Successful Bone Marrow Transplantation

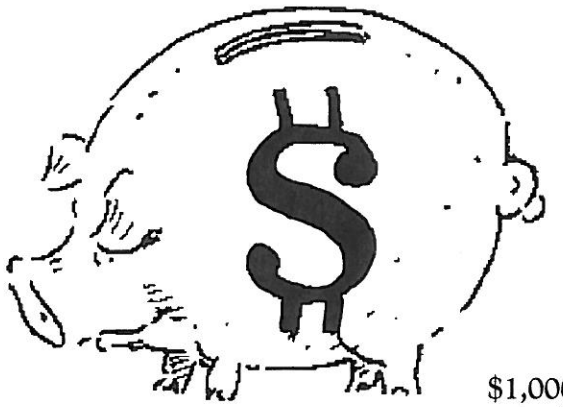
Fanconi anemia is a hereditary disease in which the genetic defect involves all the cells in the body, making this condition a multi-organ disorder. This is in contrast to certain hereditary disorders in which the deficiency or abnormality of the gene product involves a single organ. A good example is sickle cell anemia in which the genetic defect leads to the production of an abnormal hemoglobin. Since, in Fanconi anemia (all complementation groups) there is increased chromosomal breakage in all cells, presumably due to a defect in the DNA repair mechanism, all organs in the body remain vulnerable. The organs with the highest rate of DNA turnover such as the hemopoietic system, male gonads at puberty and gastrointestinal tract, are likely to sustain the greatest damage. Decreased number of blood cells and hypogonadism in males are well known complications of Fanconi anemia. Unfortunately, we have very little information about the gastrointestinal function in FA patients. Abnormal gastrointestinal function may lead to decreased absorption and transport across the gut of vital minerals, amino acids and vitamins and thus may be the underlying mechanism for the microsomia (small stature).

While successful bone marrow transplantation in FA patients restores the blood counts to normal, the chromosomal defect remains unchanged in the non-blood forming organs. Consequently, increased risk of malignancies such as squamous cell carcinoma, defective sperm production and inadequate growth and development will persist after the bone marrow transplantation. It is hoped, however, that with continued research in the mechanism of the DNA damage, whether due to a defect in DNA repair or inadequate detoxification of oxygen-free radicals or perhaps some other unknown mechanism, we may be able to remedy some of these major problems.

N.T. Shahidi, MD
University of Wisconsin, Madison Medical School



The big problem with your illness, Mr. Hawkins, is that nobody famous has caught it yet.



Family Fundraising Efforts

In 1992, forty-five of the 256 families in our support group gave generously to our efforts through fund-raising activities and individual contributions. We are infinitely grateful for your help! Thanks to you, we have been able to assist worthy research projects. Because of you, research is moving ahead at a rapid pace. Each individual contribution, large or small, has helped make a difference. Please continue your efforts!

We report here on funds raised in 1992. Many families raised substantial sums in previous years which were reported in earlier newsletters.

Over $125,000:
Dave and Lynn Frohnmayer

$25,000 — 30,000:
Phyllis Cafaro

$20,000 — 25,000:
Deane Marchbein and Stuart Cohen
Ron and Fredi Norris
Robert and Linda Scullin

$10,000 — 15,000:
Bill and Pat Danks

$5,000 — 10,000:
Robert and Jennifer Kiesel
Leonard and Jan Riley
Terry and Theresa Robertson

$1,000 — 5,000:
Andrew and Vicki Athens
Pamela Baxter
Michael and Diane Bradley
Delores, Carol and Paula Ceresa
James and Donna DellaRatta
June Delvalle
Mary and Pat DiMarino
Sidney and Ethel Farkas
John and Karilyn Kelson
Bill and Jackie Lucarell
Marlene Stone
Martin and Linda Sankey
Craig and Stephanie Melancon
Mark and Susan Trager
Marc and Sandy Weiner

$500 — 1,000:
Ed and Barb Brookover
Greg and Diane Hayes
George and Kathy Reardon

Up to $500:
Diana Fitch and Darryl Blecher
Monte and Renee Clendening
Dottie Day
Buff and Dulcy Delcamp
Delbert and Linda Dotson
Ed and Janice Duffy
Pamela Fadeley
James and Doris Galvin
John and Irene Kalman
Leardon Keleher
Lynn Lecuyer
Gayle Licari
Joe and Lynn Linsenman
Jack and Pamela McCarty
Griff and Cecilia Morgan
Kevin and Lorraine O'Connor
Daniel and Bonnie Rosen

We also report, with gratitude yet great sadness, that contributions were received in loving memory of Scott Bradley, Robby Beck, Cindy Lawrence and Avi Weiner.

Thanks Kelsons!!!

On June 10, 1992, **John** and **Karilyn Kelson** held a fundraiser, with the help of the Channing Day School and All Souls Unitarian Church. The event included "desserts and drinks, games, music and magic for the children" and raised over $3,000 for FA research. Karilyn Kelson later wrote:

"Everything was donated, and it really was a fun party. I feel we were wonderfully successful for a first try...Thanks for your letter which got us motivated to try our hand at fundraising. It was a difficult but rewarding plunge – not only for the money, but for the kindness and support shown to Lauren and our family by the organizers and participants of this event. The evidence of Lauren's impact on people was very moving to us."

Anxiety does not empty tomorrow of its sorrow, but it does rob today of its strength.
-Anonymous

Unrelated Marrow Donor Recruitment: Update

In a mere five years, the National Marrow Donor Program (NMDP) has recruited 786,808 volunteer marrow donors. Each month, between 15,000 and 30,000 new names are added to the registry. Dave Frohnmayer, Advisor to the Board of the Fanconi Anemia Research Fund, is also a founding member of the Board of Directors of the NMDP. Dave offers these observations:

(1) The primary focus of the NMDP donor recruitment efforts is now on ethnic minorities. Properly so. This is because HLA tissue types are inherited and descend through genetic lines. Far fewer ethnic minorities are represented in the NMDP than are needed to find matching donors for minority group patients.

(2) The vast majority of marrow donor volunteers presently are of Caucasian extraction. It is therefore relatively unlikely that a person of Caucasian descent will be matched by a new recruit if a matching donor does not presently exist in the NMDP registry.

(3) If you are considering a donor recruitment drive because the FA patient or prospective donors are from an ethnic minority population, you should contact: Jack Packer, Assistant Director for Minority Recruitment (1-800-526-7809). Federal funding is available for tissue typing the following ethnic groups: African American, Hispanic, Asian or Pacific Islander and American Indian or Alaskan Native.

Special Gifts

This year brought extraordinary acts of generosity from our FA families and friends. We mention a few:

An FA family, who wishes to remain anonymous, paid the round-trip airfare so that a mother of FA children could attend the Family Symposium in Orlando.

Karen Frohnmayer, cousin of **David Frohnmayer**, married **Todd Van Horne** last spring. In lieu of wedding presents, Karen and Todd requested that contributions be made to the FA Research Fund, Inc.

Leonard and **Jan Riley** mailed a successful fundraising letter to their friends and relatives this past year. Their daughter, **Alaina**, underwent a successful marrow transplant in August, 1991. They write: *"Those of us who have escaped the ultimate misfortune of losing a child feel a special responsibilty to step forward and to assist in finding a cure for this rare and deadly disorder.... We also know that scientific research could greatly improve the long term prognosis for our precious daughter."*

Martin Sankey continues to donate his time and skill in preparing this newsletter; the American Greetings Corporation generously donates staff time and resources for this publication.

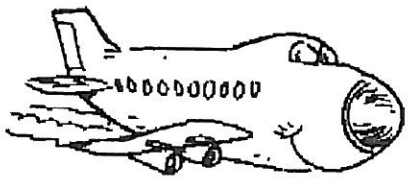
We are deeply grateful for these special gifts!

FA Family Handbook

As part of our pledge to the Meyer Memorial Trust, we have written a handbook for families affected by Fanconi anemia. You will receive a copy soon.

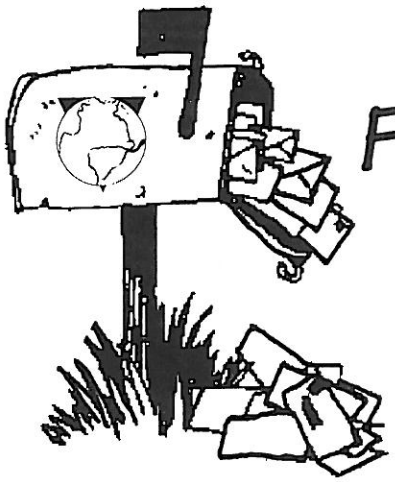
Respected scientists strongly encouraged us to develop this resource and have helped with this effort. As our understanding of FA increases and as new therapies become available, we plan to revise this handbook.

Please read this booklet critically. Does it meet your needs? What important questions does it fail to address? What would you add, delete or change? Let us know. Whenever possible, we will use your suggestions as we update this handbook periodically.



Free Medically-Related Travel

If you are flying to another city with your child for his/her medical treatment, please let us know. We have been successful in securing complimentary flights for FA patients and their parents. We would like to assist you, should you have this need. Contact **Linda Solin**, (503) 687-4658 at the FA Research Fund office.



From Our Families

According to statistics presented at our November, 1992 scientific workshop, only 30% of FA patients transplanted from matched, unrelated donors are long-term survivors. Against this poor prognosis, we include letters from two families whose FA children recently had successful, unrelated transplants. Both were in relatively good health at the time of transplant, which could have improved their chances for survival. These letters speak of courage and determination in the face of difficult obstacles; they bring hope to many of us.

Kelly Turner

We returned to New Zealand on November 10, 1992 after a 10 month stay in Paris, France with our 9 year old daughter, Kelly, who had a successful unrelated bone marrow transplant at St. Louis Hospital.

To enable Kelly to have this transplant, we spent 18 months publicly raising approximately $230,000, because in New Zealand we have a public health system.

Professor Eliane Gluckman searched the French Bone Marrow Registry and found an HLA match for Kelly. When we left for Paris on January 10, 1992 Kelly's blood counts showed white cells of 3.8, hemoglobin of 9.0 and 36,000 platelets. She had not received any blood transfusions or drug therapy. Apart from her low blood counts she was in good health and spirits.

At St. Louis Hospital Kelly's pre-transplant conditioning regimen went well and we were very relieved. The transplant of marrow was administered on February 14, Valentine's Day. As we call it, "the ultimate gift from an unknown man"! Within 2 weeks Kelly's white cells went up to 3.0. She celebrated her 9th birthday on March 22 and around that time her blood counts plummeted. A lung infection was detected and treated and Kelly was started on GM-CSF to stimulate her white cell growth. Within a week her white cell count again rose. She continued to have red cell and platelet transfusions. The lung infection decreased but Kelly was kept on GM-CSF as each time they attempted to stop it her white cell count plummeted very low. Just before her discharge from the hospital on April 22, she was found to have a cytomegalovirus infection in her blood which explained the problems with the counts. Kelly was still released from the hospital and stayed with us in a tiny apartment. Twice a day nurses from a home hospital service visited Kelly and gave her an intravenous gancyclovir drug to treat the virus. A doctor visited three times a week to give platelet transfusions, and red cells every

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Clay Eubanks

On December 27, 1991, my son, Clay, age 16, was diagnosed with Fanconi anemia. On September 17, 1992, he entered the University of Minnesota Hospital for an unrelated bone marrow transplant.

After much thought and soul-searching, Clay made the decision to go for the transplant shortly after he was diagnosed. Clay chose to have the transplant while he was still in very good physical shape. He told us that "he just didn't want a few years...he wanted his life". Some of you have met Clay and know of his incredible attitude and his will to live. He entered this procedure with a very positive attitude. The combination of this attitude, a closely matched donor, and the skill and care

> "You do your job and I will do mine and I will walk out those doors."
> *Clay Eubanks*

of his team of doctors have afforded Clay a second chance at life.

We started a very intense search to determine to whom we would entrust Clay's life. We talked with many doctors, read everything we could get our hands on, and talked with other families affected by FA. Clay talked and met with everyone his father and I did. But the final decision was his to make. After much research, thought, and prayer, we chose the University of Minnesota Hospital.

The first day we arrived at the Hospital, a team of doctors met with us and explained everything in detail. When they got through, they asked Clay if he wanted to back out. If he did,

Continued on next page

Kelly Cont'd.

two weeks. We also visited the day hospital and Professor Gluckman regularly.

Kelly Turner

After three weeks Kelly's intravenous treatment was changed to a drug called foscanet, along with 500 mls of 2.5 glucose hyperhydration per treatment because of the drug's toxicity. This treatment was continued until June when the virus was cleared from the blood. Kelly also developed a GVH rash on her skin which was soon controlled with an increase in prednisone and cyclosporine. Kelly remained infection free and the GM-CSF was discontinued on July 17. Her white cell count stabilized at 2.0. Kelly continued to need red cell and platelet transfusions which gradually became less frequent. The prednisone caused a minor diabetic problem which was controlled with insulin. By November our funds were very low and Professor Gluckman was pleased with Kelly's progress and said she was stable enough to return to New Zealand.

Kelly's latest blood counts show white cells of 11.0, hemoglobin of 11.2 and 30,000 platelets. Presently she is not requiring any blood transfusions. Kelly is to remain on prednisone (currently 10 mg per day) and cyclosporine (currently 20 mg per day) for another 6 months. Kelly's specialists keep in close contact with Professor Gluckman.

We feel very grateful that Kelly's transplant was successful. It may give new hope to other families considering the same option we chose. We were extremely fortunate to have wonderful support from the French FA families. They even helped us fundraise when our funds became low. Life would have been very difficult without their help. We also met many FA families from other countries. Although there was often a language problem, we managed to communicate in various ways. When you have FA in your family there is an unspoken empathy anyway, no matter what language you speak.

We found Professor Gluckman to be not only clever in her field but supportive to us whenever we had any concerns. It was not easy being amongst a foreign culture for so long especially when we weren't fluent in French, but we managed. We were also separated from our 12 year old son, Daniel who remained in New Zealand with his Aunty. But we knew it was important that Kelly receive the specialist care for as long as possible.

Kelly is looking forward to returning to school in February, 1993 after our Summer holidays. We are hoping 1993 will be a good year for our family and wish the same for all other FA families.

Kind regards,

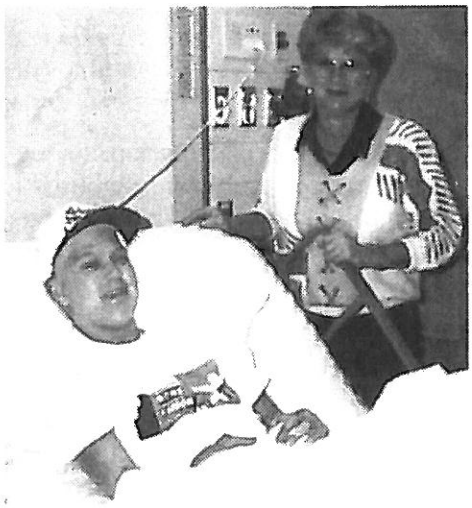
Richard and Jan Turner

Clay Cont'd.

now was the time. He would lose his chance once they started treatment. Clay replied, "You do your job and I will do mine and I will walk out those doors" - and that he did.

Caregivers at the University of Minnesota Hospital work in teams. Everything they do, they do with unconditional love and dedication. I cannot say enough about the doctors, the nurses and the staff. When Clay had a good day, they had a good day with him. When he had a bad day, they were there for Clay and our entire family. The second they detected a problem, they reacted quickly to it.

Clay, his sister Staci and I arrived in Minnesota as strangers and now we feel we have a new family. You become part of the hospital family. They offer many, many services for the entire family. Clay was able to continue his school work which was very important to him. He wants very much to graduate with his class. The hospital offers a program called "CARE". It was a lifesaver for us. A person is assigned to you just to "be there" for you and to help in any way possible.



Clay (l) and Kay Eubanks (r).

The facilities in Minnesota are wonderful. They extend beyond the hospital. We stayed at the Ronald McDonald House until we could obtain an apartment near the hospital. The staff and the facility at Ronald McDonald are unbelievable. During this stressful time, it was wonderful to have this place as a comforting retreat. The staff continued to give us support and varied services well after we moved into our apartment. Clay now wants to volunteer for work at the Ronald McDonald house in our home town of Tallahassee, FL.

The day Clay was discharged from the hospital was extremely emotional. Our prayers were answered and we were elated with Clay's success. But it was very hard to leave behind the group of people who gave Clay his life back and supported Staci and me emotionally. We will carry them in our hearts forever.

Conclusion on page 8

We received this very poignant letter and poem from **Dr. Giovanni Pagano**, researcher and father of an FA son. His words touched us deeply; we share them with you.

Letter From a Father

A trip across the families affected by the loss of a child or concerned by a deadly disease threatening theirs. The major pain is for children themselves, those we lost, finding no human word for consolation. Other unhappiness is to see others in need of help and to realize that some of them may be helpless. Luckily enough, it is also clear that many of these children will be saved, either by currently available cures or by research progress. Thus, not all the affected children are in real trouble, since many of them live a normal or quasi-normal life, sometimes a happy and rewarding one. Thanks to current and future cures, these children and young adults will lead disease-free lives.

Meeting parents, especially mothers, is another matter. Altogether, we reach an invaluable goal, being a community and banning everyone's isolation; thus we can encourage each other, and avoid despair.

However, many mothers remain with their grief and concern encompassing their own children no matter how healthy they are, since they feel themselves linked to the other children who were lost or are currently endangered. Every loss is painful to all of us, yet the mother feels the death of "another" child as an evil warning for her own. And she weeps, losing the most reasonable expectation that science will help. No matter how sound the reasons for hope you can give her, no matter how informed she is, she tends to fear the worst and cries.

I happened to be faced with these grim sights and views more than once across this trip in our inferno. I was to keep my eyes dry, even in the most painful circumstances. Dry, but not indifferent eyes, with a deep love for all these friends, the mothers of "our" children, who shall be helped to hope.

The Crying Angel
Naples, December 8, 1992

My dear friend, bride, mother, sister,
you crying angel
I find myself steering you to hold your
hand and caress you
On me the flaming veil of your grief is
a hood
Which my voice and glance cannot
go through
With my open wounds I must keep
dry my eyes
And together we'll climb above the
abyss line
Again to see the starling crowns
embroidering the sky

Clay *(Continued from page 7).*

I look forward to the day I fly back to Tallahassee with my son and daughter by my side. The heroic act of a donor and the people at the University of Minnesota Hospital will have made it all possible.

I asked Clay and Staci how Clay's illness had affected them. They both said it had made them more caring. They know especially what REALLY counts in life. What a different world this would be if we all could have learned that at 16 and 13 years of age.

I went to Minnesota with two children and I came home with two adults. There is a song that goes "...I'm leaving here a better man..." This is so true for Clay, not only physically but mentally as well. In fact, we all did.

Kay Eubanks

Workshop *(Continued from page 1)*

- Several scientific collaborations among important researchers were established during this conference. This outcome is precisely what we encourage through our hard-earned research dollars.
- Development of an FA mouse or other animal models will provide ideal ways to study why a defective FA gene produces so many problems. These studies are crucial. They need our continuing support.
- Marrow transplantation and other therapies now promise life-extending opportunities where few existed a short decade ago.

So much remains to be done! The enclosed NIH scientific summary contains recommendations for further research. We ask your undivided attention to our fundraising goals so we can support crucial projects.

The funds you and caring organizations can raise really matter! We take pride in how quickly our very focused research dollars have achieved results.

We thank the Mobil Oil Foundation, Chiles Foundation, Collins Medical Trust, SS Johnson Foundation, Georgia Pacific and Ortho Pharmaceutical for their very generous support of this highly successful scientific workshop.

Sandy Weiner writes with love, humor and sadness of the life and early death of their son, Avi. Many of us will benefit from her kind offer to establish a support group for parents who have lost a child.

Avi Weiner was a child who, despite several birth anomalies and 17 operations, loved life to its fullest capacity and brought joy to all who had the privilege to know him.

Avi's love of music was evident at a very early age. By 2–1/2 years, he could imitate almost any tune on key. Sometimes he would wake up in the middle of the night, and we'd hear him singing sweetly to himself for an hour or two.

But he was first and foremost a comedian. Perhaps to compensate for his delayed development and small size, he was always "going for the laugh". Because of two painful and ultimately unsuccessful hip operations, he didn't walk until he was almost four years old. His motivation for walking was a whoopee cushion. When visiting a friend, he took a few steps alone and plopped down on the whoopee cushion in hysterical giggles. At his fourth birthday party, he showed off his walking ability by walking back and forth between a dozen whoopee cushions. We put one into each child's goody bag.

Eating was another area of difficulty for Avi. He compensated by being a comedian - playing tiddly winks with his cheerios, "smoking" his fishsticks, and using ziti as "fingernails".

Avi's laughter was so wonderful, he made even total strangers smile. He overcame all of the difficulties in his life with humor, song and sweet love.

We were all shocked by his sudden death on May 24, 1991. We had almost no warning - he was sick with headaches and vomiting for only one week. We didn't realize it was a brain tumor until he was gone.

Although brain tumors are <u>extremely</u> rare in FA, I feel an obligation to share with you the warning signs that Avi had: recurring sharply painful headaches accompanied by vomiting, excessive sleeping and shallow breathing.

Of course, all of these are usually <u>not</u> symptoms of a brain tumor. However, had we known Avi's diagnosis earlier, we could have spared him a lot of pain in his final hours. Although we could not have saved Avi's life, perhaps we can help save another through early diagnosis.

I am interested in starting a support group by mail or phone with other parents who have lost an FA child. We all share a most unfortunate common bond, and I feel we can help each other.

Please write or call:
Sandy Weiner
21-16 Croton Lake Rd.
Katonah, NY 10536
(914) 232-0385

"In this sad world of ours, sorrow comes to all, and it often comes with bitter agony. Perfect relief is not possible, except with time. You cannot now believe that you will ever feel better. But this is not true. You are sure to be happy again. Knowing this, truly believing it, will make you less miserable now. I have had enough experience to make this statement."

-Abraham Lincoln

FA Research Support: 1992 Update

Our Fund continues to support worthy projects to advance FA science. As our cover story demonstrates, your efforts in raising funds have made a real difference! This report supplements the account of our research activities contained in Newsletter #11, page 3 (January, 1992).

A total of twelve research projects have received financial assistance from our Fund. Eight projects involved genetic research and four were directed toward developing FA therapies.

Our Fund has granted a total of $880,486 (including $96,453 granted prior to our official incorporation).

The following grants were awarded during the year ending December 31, 1992:

James Boyd, Ph.D.
University of California, Davis
Gene cloning using the drosophila (fruit fly) organism
$50,000

Manuel Buchwald, Ph.D.
Hospital for Sick Children, Toronto, Canada
Functional complementation studies for identification of additional FA genes
$30,000

Manuel Buchwald, Ph.D.
Hospital for Sick Children, Toronto, Canada
Development of an FA mouse model to study the FA protein defect in complementation group "C"
$30,000

M. Stephen Meyn, M.D., Ph.D.
Yale University
cDNA complementation study for gene discovery
$53,028

Robb Moses, M.D.
Oregon Health Sciences University
Molecular studies in FA, including FA cell repository, complementation studies and linkage analysis
$69,820

FA Fellowship - Dr. Banerjee
University of North Carolina, Chapel Hill
Gene cloning studies for FA
$25,000

Total of grant awards in 1992:
$257,848

Our Fund supported the laboratory of **Margaret Zdzienicka, Ph.D.** of The Netherlands throughout 1992. Since this grant was awarded in late 1991, it is not included in the above total. As this edition goes to press, the Board of Directors is considering additional requests for research support.

Experts Join Scientific Review Board

We are pleased to announce the selection of four distinguished scientists as additional members of our Fund's Scientific Review Board. These experts review grant proposals and make recommendations to our Board concerning funding priorities. We are deeply grateful for this generous service to the FA cause.

O. Michael Colvin, M.D., Professor of Oncology and Medicine at Johns Hopkins Hospital, is an internist specializing in the pharmacology of bone marrow transplants.

Nancy J. Carpenter, Ph.D. is a microbiologist for the Chapman Institute of Medical Genetics at Children's Medical Center in Tulsa. Her laboratory also does FA diagnostic DEB testing.

Susan Wallace, Ph.D. is the Chairperson and a Professor in the Department of Microbiology at the University of Vermont. She is an expert in the field of DNA damage and repair.

Hans Joenje, Ph.D. is an expert in the fundamental aspects of chromosomal instability, oxygen toxicity and related phenomena. He is an Associate Professor at the Institute of Human Genetics at Free University, The Netherlands.

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Oops!

The editors mistakenly identified N.T. Shahidi as the author of the article "Toxic Agents to Avoid", which appeared in our last newsletter. It was in fact written by our own Board member, **Joyce Owen, Ph.D.** Our apologies to Joyce!

FA family newsletter

Fanconi Anemia Research Fund, Inc.
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Coordinator: Linda Solin
Family Support Coordinator: Lynn Frohnmayer

DON'T MISS OUR THIRD ANNUAL FAMILY SYMPOSIUM!

July 16, 17 and 18 in Bloomington, Minnesota

- Meet other FA Families
- Gain and Give Support
- Learn from Other Parents
- Hear from Experts Concerning the Latest Developments in Treating FA
- Have Fun! Explore CAMP SNOOPY, LEGO IMAGINATION CENTER, GOLF MOUNTAIN
- Provide Peer Support for your Child in a Loving and Fun Environment

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REPORT

Workshop on Molecular, Cellular, and Clinical Aspects of Fanconi Anemia

This workshop, held November 23-24, 1992, in Bethesda, Maryland, was intended to serve as a forum for assessing the current state of knowledge on the basic and clinical aspects of Fanconi anemia and to provide the National Heart, Lung, and Blood Institute and the Fanconi Anemia Research Fund with recommendations for research to help ensure continued advances in the diagnosis, treatment and prevention of this disease.

The workshop consisted of twenty-three scientific presentations in five sessions that covered a broad spectrum of areas ranging from fundamental knowledge at the genetic, molecular, and cellular levels, to current and future therapies. Twenty-eight additional presentations were included in an evening Poster Session. One hundred people attended, including twenty from outside the United States, including Canada, United Kingdom, France, Italy, Brazil, The Netherlands, and Germany. A Program Book containing the program, speaker and poster abstracts, and list of registrants was distributed in advance of the workshop. At the completion of the workshop, the Scientific Organizing Committee, Session Chairpersons, and sponsors met to discuss the highlights of the workshop and to propose specific recommendations for future research. The following pages represent the summary of these discussions.

Cell and DNA Damage and Repair in Fanconi Anemia

Fanconi anemia is a complex genetic disorder characterized by multiple congenital malformations, bone marrow failure, elevated sensitivity to DNA damaging agents and an increased susceptibility to the development of malignancies. The altered sensitivity to particular DNA damaging agents, such as diepoxybutane (DEB), has been a consistent and central observation in the diagnosis of Fanconi anemia. This increased sensitivity has been crucial in the isolation of the Fanconi anemia complementation group C gene [FA(C)], and in our current understanding of the likely pathogenesis of Fanconi anemia.

Dr. Auerbach presented evidence from a large series of DEB tests that Fanconi anemia probands and affected siblings have an elevated and similar level of DEB-induced chromosome aberrations. The DEB test can accurately distinguish spontaneous aplastic anemia from hereditary cases, and from the VATER syndrome, a nonrandom association of congenital defects. The DEB test is also useful for prenatal diagnosis by amniocentesis

or chorionic villus sampling. Details of quality control, such as failure rate of the assay, false positives or negatives, etc., and comparison with other assays, were not presented.

Oxygen, although essential for cell growth, is also toxic to cells in vivo or in vitro, as explained by Dr. Joenje. Standard conditions for cell culture in air (20 percent 0_2) expose cells to considerably higher 0_2 concentrations than in most body tissues. A variety of cellular damages are produced by toxic oxygen species including damage to proteins, lipids, and DNA. A number of investigators have observed Fanconi anemia cells to be more sensitive to standard 0_2 conditions of cell culture and that this sensitivity can be ameliorated by a reduction in 0_2 tension. However, there are a number of questions regarding the relationship of this effect to Fanconi anemia. For example: Is this effect consistent for all Fanconi anemia cells and Fanconi anemia complementation groups? Does the hypersensitivity to 0_2 of Fanconi anemia cells involve DNA damage?

While Fanconi anemia cells are clearly hypersensitive to the cytotoxic and clastogenic effects of DNA-damaging agents, the evidence that Fanconi anemia cells are deficient in DNA repair per se, rather than in some later response to DNA damage, remains inconclusive, according to Dr. Henner. The correlation between an agent's ability to produce DNA-DNA crosslinks and increased toxicity for Fanconi anemia cells, suggests that Fanconi anemia cells may be defective in a specific mechanism for repair of DNA-DNA crosslinks. Fanconi anemia is one of several hereditary diseases with defective repair and response to DNA damage. The multiple complementation groups in each of these diseases and biochemical evidence indicate that there exist distinct repair pathways for bulky adducts, crosslinks and non-bulky base damage. Emerging molecular, genetic and biochemical systems can now be combined to elucidate the biochemical nature of the putative Fanconi anemia DNA repair defect.

Molecular Genetics of Fanconi Anemia

Discussions focussed on a variety of approaches used to isolate genes defective in Fanconi anemia, including homology cloning of the Fanconi anemia A gene or FA(A), genomic DNA transfer to complement the Fanconi anemia cellular defect using an FA(D) cell, cDNA expression libraries to clone the FA(C) gene, and linkage analysis to locate the FA(A) gene to chromosome 20q.

The presentations highlighted the difficulties inherent in the isolation of genes of unknown function. To date, the only successful outcome has been the isolation of the FA(C) cDNA, though some of the other attempts may be close to fruition.

Dr. Boyd presented data suggesting that the Drosophila mus308 genes may be analogous to the FA(A) gene. On the basis of the data presented, it is likely that Dr. Boyd should be able to clone the mus308 gene within the coming months. He is using the classical positional cloning method in an attempt to clone the mus308 gene for subsequent use in the

identification of the human homolog. However, extensive sequence diversity between Drosophila and man may preclude isolation of the human homolog. Thus, it may be necessary to use "evolutionary walking" and go through intermediate species.

Dr. Zdzienicka presented her results on cloning of the human gene that corrects the defect in hamster V-H4 mutant cells. On the basis of somatic cell hybridization studies, she has shown that V-H4 mutant cells do not complement the defect in FA(A) cells, while they do complement FA(B) cells. The approach taken is to introduce human genome DNA together with a positive selection vector (gpt or neo), select gpt-or neo-resistant cells, and then look for human repetitive sequences. Overall, the approach of using V-H4 cells was ingenious, though it appears much more difficult than previously expected. The large size of the gene or continuous DNA rearrangements due to chromosomal instability of the cell may be factors contributing to these difficulties.

Dr. Moustacchi's group described experiments aimed at cloning the FA(D) gene by genomic complementation of primary fibroblasts using mouse DNA. A lambda genomic library was constructed and screened for the presence of mouse DNA. Of 19 phages isolated, 1 provided partial complementation of the mitomycin C sensitivity phenotype of FA(D) cells. Probes derived from the mouse DNA were used to isolate cDNA that has homology to a super family of 89 kD motor proteins known to be involved in protein sorting, organization of cellular membranes, establishment of cell polarity, chromosome segregation during mitosis, and a number of developmental processes, all of which could be relevant to Fanconi anemia. They are currently attempting to confirm that this cDNA complements the FA(D) defects. This research is promising although it is difficult to understand why a phage with only a small portion of the mouse gene, and no regulatory region, should complement the FA(D) defect. Furthermore, at the cellular defect, the complementation does not extend to chromosomal instability. Thus, it is not yet evident that this cDNA corresponds to the FA(D) gene.

Dr. Auerbach discusses her studies of linkage analysis in Fanconi anemia, a project initiated in 1988 when no other approaches to clone the Fanconi anemia gene appeared viable. Under the assumption of heterogeneity, analysis of a cohort of 35 families from the International Fanconi Anemia Registry lead to the identification of a subset of families linked to a marker on chromosome 20q. Since one of these families included one which Dr. Buchwald had classified as FA(A), it was assumed that the linked gene was FA(A). After the discovery of FA(C) on chromosome 9, linkage analysis showed no linkage to chromosome 9 probes. However, heterogeneity analysis, assuming loci on 9q, 20q, and elsewhere, indicated that approximately 10 percent of families are linked to 9q, 10 percent to 20q and 80 percent to other loci. As Dr. Auerbach indicated, linkage analysis is not a fruitful approach to isolate the Fanconi anemia genes, given the number of families available and the degree of locus heterogeneity in Fanconi anemia.

Dr. Buchwald reviewed, first, the data leading to the classification of Fanconi anemia lymphoblast cell lines into four complementation groups. Given that only seven cell lines have been used, it is likely that more complementation groups exist. He then summarized the use of episomal cDNA expression libraries to clone the FA(C) gene complementation

a number of suggestions regarding the progression to myelodysplasia and leukemia based on retrospective analysis of data from the International Fanconi Anemia Registry. This point was extremely controversial and generated extensive discussion.

Hematopoiesis and Oncogenesis

This session focused on developing an up-to-date view of cellular and molecular leukemogenesis, with a particular emphasis on myeloid leukemia for which Fanconi anemia patients are at greatest risk. Control of hematopoietic cellular differentiation is a vital area of investigation for acute myeloid leukemogenesis.

Dr. Liebermann presented results of his work using murine myeloid leukemic cells that can be induced to differentiate with leukemia inhibitory factor or IL-6. This inductive factor induces early expression of a set of genes that have been cloned and sequenced. Some of the induced genes encode known factors, including junB, c-jun, and ICAM-1 as well as some novel genes such as MyD116, MyD88, and MyD118. Because inhibition of function of some of these genes inhibits expression of the full developmental program of differentiation, they play a role in governing downstream genetic events in differentiation.

Dr. Hoffman-Liebermann presented information from her work on transcription factors that inhibit the program of differentiation. Both c-myc and c-myb expression must be repressed for leukemic cells to express a full differentiation program. The tumor suppressor gene, p53, may be involved in the control of genes that regulate differentiation. Evidence was provided that both c-myc and c-myb were not only required for the IL-6 inductive effect (for differentiation), but were also required for the protective effect of IL-6 on TGFB-treated cells.

Dr. Cline presented a comprehensive overview of molecular mechanisms of leukemogenesis and in particular on the involvement of p53 in tumor progression. Evidence was presented that progression of CML to AML, CLL to Richter's syndrome, and myelodysplasia to AML, often involves p53 alterations. Such alterations could be rearrangements, deletions, or most commonly, point mutations.

Dr. Greenberger reviewed studies designed to test the hypothesis that irradiated hematopoietic stromal cells produce leukemogenic factors. The results have been positive and the effect, at least in part, seems to involve cell-cell contact between progenitors and stromal cells. He is in the process of identifying sets of genes induced in irradiated stromal cells in an attempt to identify this interesting factor.

Dr. Bagby indicated that these important studies on the mechanisms of leukemogenesis could be facilitated if bone marrow cells from Fanconi anemia patients were more readily available.

Treatment Today and Innovations for the Future

According to Drs. Gluckman and Harris, 159 bone marrow transplants for Fanconi anemia using HLA-matched related donors have been reported to the International Bone Marrow Transplant Registry. In most centers, and in Paris where the greatest number have been performed, now totaling 57, there is a 70 percent survival rate. However, in Cincinnati, where 17 transplants have been performed, a 100 percent survival rate was reported. Cord blood transplants succeeded in three out of four attempts. Using matched unrelated and mismatched family member donors, there is only a 30 percent survival rate.

Dr. Guinan summarized the total experience with cytokine treatment with either GM-CSF or IL-3 in three small groups of patients. Each cytokine produces increased neutrophils in most patients, although GM-CSF appears to be better. Only one patient from each group exhibited a red cell response, and platelets did not increase in any patients.

Dr. Liu reported results of a pilot study using recombinant human superoxide dismutase, administered by continuous intravenous infusion for two weeks in four patients. Treatment may have led to decreased chromosomal breakage but this short-term study had no impact on blood counts.

From data presented by Dr. Zanjani, it was clear that in utero hematopoietic stem cell transplantation using unmatched fetal liver cells is moving closer to reality. Currently, the degree of chimerism in the unablated recipient appears to be too low for applicability in Fanconi anemia because perhaps complete donor cell expression may be needed to prevent leukemia. More widespread use of this technique will depend on the availability of donor fetal livers.

With at least one Fanconi anemia gene available, the FA(C) gene, genetic therapy for Fanconi anemia is moving closer to human testing, according to Dr. Nienhuis. Both retroviral and the adeno associated virus (AAV) vectors containing the FA(C) gene have been prepared and are being tested for their ability to transduce and express the FA(C) gene in enriched human bone marrow stem cells. The AAV, a non-pathogenic parvovirus, offers great potential and is currently being developed for therapeutic gene transfer in patients with Fanconi anemia.

Recommendations

The following recommendations have been grouped into clinical or basic research categories. No attempt has been made to prioritize the recommendations.

Clinical Research

1. **Diagnosis and Prevention:** Prior to universal acceptance of the DEB test for diagnosis and prenatal testing of Fanconi anemia, a prospective, multi-institutional study is needed to: (a) verify the sensitivity, specificity, reproducibility, and reliability of the DEB test; (b) compare this test to others such as mitomycin C or flow cytometry detection of differences between normal and Fanconi cells in cell cycle progression; and (c) explore the use of other cells such as urine epithelial cells, buccal scrapings, or skin fibroblasts instead of lymphocytes.

2. **Natural History and Leukemogenesis:** A controlled, prospective study is needed to determine the length of time from the diagnosis of Fanconi anemia to the development of myelodysplasia and leukemia and the percent of patients that undergo this transformation, so that treatment options can best be utilized.

In conjunction with this study, the potential exists to identify early genetic events required for leukemogenesis and to distinguish them from epiphenomenal genetic events using both gain-of-function and loss-of-function analysis.

3. **Treatment:** Randomized, controlled, bone marrow transplantation trials should be performed to answer the following questions: When should a transplant be performed? Does a clonal cytogenetic pattern without increased blasts require a transplant, particularly if the procedure will utilize a matched unrelated donor? What is the correct Cytoxan dose (or other preparative agent) for each patient, each type of transplant, and each patient condition (e.g. "preleukemia")? Is irradiation helpful, or necessary? Does ATG have a role? Is methotrexate needed for prevention of GVHD? Will better HLA typing by DNA improve matched unrelated donor transplants? Is the incidence of post-transplant malignancies increased in Fanconi anemia patients? Do androgens per se impact on transplantation?

Basic Research

4. **Gene Transfer:** Efforts are required to isolate and enrich $CD34^+$ cells from Fanconi anemia marrow. Before doing human gene therapy, it would be of interest to introduce the FA(C) gene into these Fanconi anemia hematopoietic stem cells and evaluate the effects in culture. It will be important to determine whether transfected cells have a selective advantage in the host and whether the residual (untransfected) cells still give rise to aplasia, myelodysplasia, or leukemia.

5. **Gene Identification and Function:** Although the FA(C) gene has been identified and cloned, research must now be directed at:

(a) isolating other genes responsible for Fanconi anemia, including the identification of other complementation groups. Subsequent to Fanconi anemia gene identification and cloning, research efforts must be devoted to

(b) clarifying the role of Fanconi anemia genes in hematopoietic stem cells, progenitor cells, auxiliary cells, and in non-hematopoietic cells. areas of particular interest would include the linkage of the Fanconi anemia genes with the expression of genes that encode growth and inhibitory factors and their receptors; signal transduction molecules; and transcription factors, oncogenes and tumor suppressor genes; and finally,

(c) defining the relationship between the molecular defects in the proteins encoded by the Fanconi anemia genes and the clinical features of the disease.

6. **Animal Models:** In order to exploit the landmark advances made at the molecular level, especially the cloning of the FA(C) gene, it is extremely important to support research aimed at establishing animal models for Fanconi anemia.

7. **Cellular Models:** Studies of genetically heterogeneous Fanconi anemia cell lines are unlikely to provide conclusive results regarding the hypersensitivity of Fanconi anemia cells to either oxygen or DNA crosslinking agents. Experiments with isogenic cell line pairs constructed by transfection of Fanconi anemia genes from the proper complementation groups will be needed to elucidate the biochemical mechanism of these sensitivities.

8. **Sensitivity to Oxidizing Agents:** It is important to determine the precise role of oxidizing agents and antioxidants in the clinical pathology of Fanconi anemia. Animal and cellular models of the disease will facilitate such studies.

9. **In Utero Treatment:** Additional research should focus on fetal tissue transplants into fetuses in an effort to improve the degree of chimerism. It will be important to determine whether all Fanconi anemia cells need to be eliminated in order to prevent leukemia, aplastic anemia, or myelodysplastic syndrome.

10. **Cytokines:** Research is needed to evaluate the mechanisms responsible for the synergistic effects of cytokines on normal cells. Since many patients with marrow failure, especially Fanconi anemia, have hematopoietic progenitor cells that are notorious for their poor growth characteristics, investigations are needed using different cytokine combinations to stimulate the growth of such cells, first in vitro, and subsequently in human clinical trials.

11. **Hematopoiesis:** Proteins that control lineage specificity, such as GATA-1 or NF-E2 for the erythroid cells, are very intriguing. Future research in this area could focus on the actual mechanism of regulation of erythroid lineage-specific DNA-regulatory proteins and their mechanisms of action would be important in order to answer questions such as, what determines lineage commitment to neutrophil, monocyte, megakaryocyte and lymphocyte differentiation?